Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cutpoints-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine

Nordestgaard, Børge G ; Langsted, Anne ; Mora, Samia ; Kolovou, Genovefa ; Baum, Hannsjörg ; Bruckert, Eric ; Watts, Gerald F ; Sypniewska, Grazyna ; Wiklund, Olov ; Borén, Jan ; Chapman, M John ; Cobbaert, Christa ; Descamps, Olivier S ; von Eckardstein, Arnold ; Kamstrup, Pia R ; Pulkki, Kari ; Kronenberg, Florian ; Remaley, Alan T ; Rifai, Nader ; Ros, Emilio ; Langlois, Michel

Abstract: AIMS To critically evaluate the clinical implications of the use of non-fasting rather than fasting lipid profiles and to provide guidance for the laboratory reporting of abnormal non-fasting or fasting lipid profiles. METHODS AND RESULTS Extensive observational data, in which random non-fasting lipid profiles have been compared with those determined under fasting conditions, indicate that the maximal mean changes at 1-6 h after habitual meals are not clinically significant [+0.3 mmol/L (26 mg/dL) for triglycerides; -0.2 mmol/L (8 mg/dL) for total cholesterol; -0.2 mmol/L (8 mg/dL) for LDL cholesterol; +0.2 mmol/L (8 mg/dL) for calculated remnant cholesterol; -0.2 mmol/L (8 mg/dL) for calculated non-HDL cholesterol]; concentrations of HDL cholesterol, apolipoprotein A1, apolipoprotein B, and lipoprotein(a) are not affected by fasting/non-fasting status. In addition, non-fasting and fasting concentrations vary similarly over time and are comparable in the prediction of cardiovascular disease. To improve patient compliance with lipid testing, we therefore recommend the routine use of non-fasting lipid profiles, whereas fasting sampling may be considered when non-fasting triglycerides are >5 mmol/L (440 mg/dL). For non-fasting samples, laboratory reports should flag abnormal concentrations as triglycerides 2 mmol/L (175 mg/dL), total cholesterol 5 mmol/L (190 mg/dL), LDL cholesterol 3 mmol/L (115 mg/dL), calculated remnant cholesterol 0.9 mmol/L (35 mg/dL), calculated non-HDL cholesterol 3.9 mmol/L (150 mg/dL), HDL cholesterol 1 mmol/L (40 mg/dL), apolipoprotein A1 1.25 g/L (125 mg/dL), apolipoprotein B 1.0 g/L (100 mg/dL), and lipoprotein(a) 50 mg/dL (80th percentile); for fasting samples, abnormal concentrations correspond to triglycerides 1.7 mmol/L (150 mg/dL). Life-threatening concentrations require separate referral for the risk of pancreatitis when triglycerides are >10 mmol/L (880 mg/dL), for homozygous familial hypercholesterolemia when LDL cholesterol is >13 mmol/L (500 mg/dL), for heterozygous familial hypercholesterolemia when LDL cholesterol is >5 mmol/L (190 mg/dL), and for very high cardiovascular risk when lipoprotein(a) >150 mg/dL (99th percentile). CONCLUSIONS We recommend that non-fasting blood samples be routinely used for the assessment of plasma lipid profiles. Laboratory reports should flag abnormal values on the basis of desirable concentration cutpoints. Non-fasting and fasting measurements should be complementary but not mutually exclusive.

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Advances in Lipid Testing: A Practical Step Forward

Neil J. Stone*

Measuring lipids and lipoproteins has been an important focus for both clinical chemistry and clinical medicine for over 75 years. Measurements from analytical ultracentrifugation *(1)* to preparative ultracentrifugation *(2)* provided invaluable insights, but were not suited for day-to-day clinical practice. Fredrickson, Levy, and Lees *(3)* used paper electrophoresis to stimulate clinical recognition in five major patterns of plasma lipoprotein excess. Known as type I, II (IIa and IIb), III, IV, and V, they represented distinctive phenotypes, not genotypes. The shorthand notations, however, provided insight into an individual patient's lipoprotein disorder, whether due to acquired and/or genetic causes.

Yet a non–ultracentrifuge-based methodology was needed to quantify LDL cholesterol (LDL-C) concentrations in clinical practice *(1)*. The Friedewald formula allowed LDL-C determination by using a fasting total cholesterol, HDL-C, and triglycerides/5 (when triglyceride concentration was expressed in mg/dL) with the caveats that it could not be used if triglycerides were ≥400 mg/dL (4.5 mmol/L) or the rare type III abnormality was present *(4)*. This formula continues in widespread use today, but up until the recent guidance from this consensus panel has required a fasting lipid sample.

In this issue of *Clinical Chemistry*, a prominent international panel argues persuasively that fasting is not routinely required for lipid determinations *(5)*. The panel notes that nonfasting lipid panels provide practical benefits for clinician, patient, and clinical laboratory alike; have been used successfully in population cohort studies as well as randomized controlled trials of statins; and have been used in Denmark since 2009. They show data to indicate similar prognostic value for mean values for lipids whether fasting or not. They provide guidance for when a fasting lipid panel may be required and list thresholds for interpreting nonfasting lipids and lipoproteins for laboratory reports for patient and clinician.

Is nonfasting an advantage over traditional lipid thinking? It is important to note that although the 2013 American College of Cardiology/American Heart Association cholesterol guidelines preferred fasting lipids, they acknowledged that nonfasting lipids could be used. They noted in patients with nonfasting concentrations of non–HDL-C ≥220 mg/dL (≥5.7 mmol/L) or triglycerides ≥500 mg/dL (≥5.7 mmol/L) that a fasting sample was needed to inquire into an underlying genetic disorder *(6)*. Moreover, the lipid inputs for risk estimation in the American College of Cardiology/American Heart Association cholesterol guideline risk estimator use total cholesterol and HDL-C, which can be obtained in a nonfasting state *(7)*. Both an editorial and a recent article acknowledged, however, that whether fasting or nonfasting lipids are recommended, the choice of the specimen type depends on the question posed by the clinical situation *(8, 9)*.

Although there is no disagreement regarding routine nonfasting lipids for atherosclerotic cardiovascular disease risk determination, there still are situations for which fasting is preferred or may be required. This list includes monitoring patients with severe hypertriglyceridemia (>440 mg/dL or >5 mmol/L) and patients with hypertriglyceridemia followed in a lipid clinic, monitoring triglycerides in individuals recovering from hyperlipidemic pancreatitis, and establishing a triglyceride assessment baseline before starting medications that can trigger severe hypertriglyceridemia and risk of acute pancreatitis. Common examples of these medications include steroids, estrogens, tamoxifen, retinoic acid for acne, or L-asparaginase used in chemotherapy. Fasting lipids can make sense if a fasting blood sample was needed for other reasons. Consider patients who require a fasting blood glucose. This sample may be required to monitor the metabolic syndrome or follow individuals on statin therapy who develop increased fasting blood glucose concentrations. Using data from the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) randomized controlled trial, investigators noted progression to diabetes was more likely to occur if the statin-treated individual had major diabetes risk factors such as fasting blood glucose ≥100 mg/dL (≥5.5 mmol/L), hemoglobin A_{1c} ≥6.0% (≥42 mmol/mol), body mass index ≥30 kg/m^2, or metabolic syndrome factors, whereas it was unlikely if they did not *(10)*.

Although the panel presents data showing concordance with mean values for LDL-C measured by the

Department of Medicine/Division of Cardiology, Feinberg School of Medicine, Northwestern University, Chicago, IL.
* Address correspondence to the author at: 676 N. St. Clair Suite 600; Cardiology Chicago, IL 60611. Fax 312-926-8620; e-mail n-stone@northwestern.edu.
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Friedewald formula in fasting and nonfasting samples, a note of caution should be raised by those who use fixed LDL-C targets for clinical decision-making. This scenario is not a concern for the National Institute for Health and Care Excellence–UK guidelines *(11)* or the US guidelines *(6)*, which did not treat to fixed targets. It is a potential concern, however, for clinicians who follow the current European Atherosclerosis Society/European Society of Cardiology guidelines (as noted in Box 2 of the joint consensus statement) and use 70 mg/dL (1.8 mmol/L) as a target for high-risk patients *(12)*. Martin et al. *(13)* in a sample of >1 million patients noted that the Friedewald equation tended to underestimate LDL-C when triglyceride concentrations were ≥150 mg/dL (≥1.7 mmol/L). This result most likely occurred when triglyceride concentrations exceeded 200 mg/dL (2.25 mmol/L). Thus the use of nonfasting samples along with guidelines that advocate decision-making based on fixed targets could affect therapy decisions. Finally, many hospitals and clinics are in close proximity to restaurants. To minimize variability, patients should be counselled to avoid high-fat meals on the day of the visit.

In summary, the panel makes a strong case for routine nonfasting lipids. This is especially so for atherosclerotic cardiovascular disease risk assessment. This guidance alone should reduce morning congestion in clinical laboratories and allow the patient seen in an afternoon clinic to avoid having to return for fasting assessment. But as this report indicates, there are situations in those with increased triglycerides for which fasting is preferred and clinicians might benefit from point-of-care prompts to be sure they are understood. Finally, nonfasting lipids should be identified as such in the electronic medical record database. This step will aid clinical recognition of older data for which fasting was the norm and the newer nonfasting data. It will also aid research queries of the electronic medical record to provide further insights that hopefully will improve lipid thinking.

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